UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,506	08/10/2001	Oxana Ibraghimov-Beskrovnaya	126881201600	8221

7590 01/13/2005

Antoinette F Konski
McCutchen Doyle, Brown, & Enersen, LLP
3 Embarcadero Center, Suite 1800
San Francisco, CA 94111

EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,506	IBRAGHIMOV-BESKROVNAYA E AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-21,23-26 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,27 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented.

Misnumbered claims 15-30 have been renumbered as claims 14-29, respectively according to 37 CFR 1.126.

2. Claims 1-29 are pending.

3. Claims 1-21, 23-26 and 28 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 22, 27 and 29 are under examination as they read on a method for enhancing cell-cell adhesion in a suitable tissue, using an antibody.

5. In view of the Appeal Brief filed on 10/18/04, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, Applicant must exercise one of the following two options:
(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,
(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

6. In view of the new grounds of rejection presented below, the present Office Action is made NON-FINAL. Applicant's arguments made in the Appeal Brief will be addressed as they pertain to the new ground of rejection.

7. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional applications 60/105,876 and 60/141,175 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 22, 27 and 29 of this application. Examiner could not find any written support for the claimed method that corresponds in either of

these applications. The priority of this application deemed to benefit from the international application No. PCR/US99/25091 filed on 10/25/1999.

8. Claim 22 is objected to because it is improper to recite "Method", it is suggested that applicant insert the article "A" before the word "Method". Correction is required.
9. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 27 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The "cell-matrix adhesion " recited in claims 27 has no antecedent basis in base claim 22. Base claim 22 only recites a cell-cell adhesion. Further, the "suitable cell" recited in claim 27, has no antecedent basis in base claim 22. Base claim 22 only recites a suitable tissue.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 22, 27 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for a method for "modulating" cell-cell adhesion in any **suitable tissue**, comprising delivering to the tissue **any agent** that "modulates" the biding of polycystin in the tissue, wherein the modulation of cell-cell or cell-matrix adhesion is "promotion or enhancement" of cell-cell or cell-matrix adhesion in a suitable cell or tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The basis for this rejection is set forth in the previous Office Actions mailed 11/20/02 and 9/12/03 and is also fully set forth below.

The specification disclosure does not enable one skilled in the art to practice the invention without any undue amount of experimentation. The specification lacks empirical data on using pathogenic principles to design and test specific agents in animal models with the prospect of ultimate relevance in human disease. The status of the art that the art is unaware of successful methods with chemically analogous agents that modulates the binding of polycystin for the use in modulating cell-cell or cell-matrix adhesion, a more complete statement of how to use must be supplied.

The elected embodiment is directed to a method of promoting or enhancing cell-cell or cell-matrix adhesion in a tissue by delivering to the cell or tissue an effective amount of anti-polycystin to the tissue. The specification on page 47, lines 24-27, discloses that one can restore normal cell-cell or cell-matrix adhesion in a tissue containing soluble, mutated polycystin by removing or binding the mutated polycystin using the anti-polycystin antibodies. However, Applicant's strategy to remove or bind the mutated polycystin using anti-polycystin antibodies or any agent is fraught with inaccuracies and that these methods are still notably deficient in defining and describing the complexity of polycystin function in cell-cell or cell-matrix adhesion. The skill in the art would doubt that the claimed method would work using anti-polycystin antibodies or any agents on cell-cell or cell-matrix adhesion. First, the specification fails to disclose any antibodies or agent that would bind to a mutant form of polycystin-1 but not wild type polycystin. Second, while the specification discloses that PKD1 is a cell surface receptor or adhesion molecule (see page 2, line 30) and different anti-polycystin-1 antibodies staining demonstrate intercellular membrane localization of polycystin-1 (see pages 8-9, under Figure 11), the specification fails to point out how such polycystin molecule can be in a soluble form so that one skilled in the art can target such soluble form. Third, it cannot be seen how an antibody that targeted either a mutated or soluble form of PDK-1 would be able to enhance or promote "restore normal cell-cell or cell-matrix adhesion in a tissue" in the absence of a wild type PKD-1 in said tissue. Forth, an antibody that recognizes a soluble form of PKD-1, would cross-react with the wild-type adhesion receptor PKD-1, since they share a common epitope. The specification fails to provide antibodies that distinguish between the soluble form and the wild type form of Polycystin. Thus such antibody would have the properties of cell-cell or cell-matrix *activator* and *inhibitor*. The skill artisan would not know when to activate and when to inhibit the cell-cell or cell-matrix adhesion in the suitable tissue. It is unpredictable whether enhancement of cell-cell or cell-matrix adhesion with anti-polycystin antibodies or agents in a suitable tissue would reach an end point. It is not clear that the skilled artisan could predict the efficacy of the anti-polycystin antibodies or any agent on cell-cell or cell-matrix adhesion. The clinical value of such strategies remains to be seen. Finally, the specification does not provide empirical data to show the effect of anti-polycystin antibodies or agents on cell-cell or cell-matrix adhesion in any tissue.

The specification on page 2, line 11-26, discloses that linkage studies and mutation analysis have indicated a causative gene (PKD1) located on chromosome 16q13.3, which is responsible for 85% of ADPKD cases. A large number of mutations in the PKD1 gene sequences have been found to be associated with the onset of polycystic kidney disease. A part from large genomic deletions that eliminate PKD1, the mutations that have been defined clearly in ADPKD1 families appear to result in the transcription of a truncated or abnormal message RNA from the affected allele. These gene sequence alterations include small in-frame deletions, deletions and missense mutations that result in premature termination, splice-site mutations and chromosomal translocations which interrupt the gene. However, PKD1 gene has an unusual bipartite structure, with 70% of its 5` end duplicated in other places of chromosome 16. Another important feature of the human PKD1 gene is a cluster of two long polypyrimidine tracts in adjacent introns in the center of the gene. Polypyrididine tracts can form triple helices with diverse biological effects,

affecting gene expression and enhancing mutagenesis in variety of ways. Furthermore, the human has more than one copy of PKD1 gene, which may likely to account for at least some of the increased mutability of human PKD1, since having more than one copy of the gene can promote mutation. Finally, polypyrimidine tracts in human PKD1 may significantly contribute to the gene's overall instability. Thus the specification lacks animal studies which elucidate the etiology and pathogenesis of PKD and the related cellular and molecular mechanisms that determine kidney structure and function.

The specification on page 17, lines 11-12 discloses that "Modulation" or "modulates" of the interaction can be augmentation of adhesion (page 47, line 6) or disruption of intercellular adhesion (page 9, line 26-page 10 line 8, page 47, line 5-7). However, it is unclear whether such a desired effect can be achieved or predicted, as encompassed by the claims. In order to "modulate" cell-cell or cell-matrix adhesion, the method requires inhibiting and activating agents. Said agents are mutually exclusive in that they reach opposing endpoints, and in that they employ structurally distinct agonists or antagonists to accomplish these mutually exclusive endpoints. The specification discloses that the claimed agents can be used for both inhibiting as well as promoting cell-cell or cell-matrix adhesion. For example, the specification on page 47, lines 10- 27 discloses that the agent is any agent that inhibits polycystin-1 mediated cell-cell adhesion such agents include antibodies that bind to the Ig-like domains of polycystin or polycystin fragments comprising the Ig-like domains and agents that inhibit the expression of polycystin in a cell (e.g., antisense polycystin DNA and ribozymes that specifically recognize or cleave polycystin RNA in a cell). In addition, the specification discloses that one can restore normal cell-cell (i.e. promote cell-cell adhesion) or cell-matrix adhesion in a tissue containing soluble, mutated polycystin by removing or binding the mutated polycystin using the anti-polycystin antibodies described in the invention (see page 47, lines 10- 27). Thus, faced with contradictory and seemingly mutually exclusive function regarding the activity of the claimed antibody, undue experimentation would be required of the skilled artisan to determine the effect of anti-polycystin antibody or any agent on any particular cell-cell adhesion in vivo in view of the instant disclosure. Further, the enablement issues of making the an agent including proteins, polypeptides, polynucleotides and antibodies still remain because the specification does not teach and provide sufficient guidance as to which amino acid, nucleic acids or antibodies would retained the function of enhancing/inhibiting cell-cell adhesion. Therefore, absent the ability to predict which of these agents such as antibodies, polypeptides, proteins or polynucleotides would function as claimed, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

At issue is whether or not the claimed method for modulating/promote cell-cell adhesion in a suitable tissue, comprising delivering to the tissue an agent would function to modulate the binding of polycystin in the tissue *in vivo*. The specification discloses an assay to disrupt cell-cell adhesion in MDCK cell monolayers and aggregation with GST-Ig^{a}, GST-Ig^{b} and GST-Ig^{c} (GST-Ig^{abc}) resulted in profound disruption of intercellular adhesion (see example 10). The exemplification is drawn to the inhibition of PKD-1 interaction of the intracellular adhesion with the GST-Ig^{abc} fusion protein *in vitro*.

Since no animals were used as model system to inhibit PKD-1 mediated adhesion of epithelial cells, it.is not clear that reliance on the *in vitro* data of MDCK cell-cell adhesion accurately reflects the relative subject efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively modulate cell-cell adhesion in a suitable tissue or reach any therapeutic endpoint in mammals by administrating the therapeutic. The specification does not teach how to extrapolate data obtained from an in vitro assay studies drawn to a soluble Ig-like domains of polycystin-1 to the development of effective in vivo subject therapeutic modulation, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the therapeutic agents such as antibodies exemplified in the specification.

In addressing cell adhesion of polycystin in ADPKD kidney with cysts, Ibraghimove-Beskrovnaya *et al* (IDS reference No. 20) teach that polycystin was localized to the lateral membranes of cells in cell-cell contact (see abstract). Ibraghimov-Beskrovnaya *et al* detected variable polycystin expression in cystic epithelial, ranging from levels more intense than in normal kidney, up to the absence of staining in some cysts. As cysts in ADPKD arise from all regions of the nephron, it might be expected that all cysts from the same patient should stain either positive or negative, as they all carry the same germ-line mutation in the PKD1 gene. Ibraghmov-Beskrovnaya *et al* teach that their observation of variable staining suggests that in some cysts no polycystin expression occurs, whilst in others the normal allele is overexpressed. This former may be due to a "second hit". Ibraghmov-Beskrovnaya *et al* concluded that the significance of the variable cystic epithelial staining of multicystic dysplastic kidneys in the pathogenesis of this heterogeneous group of conditions remains to be determined (see page 6402, 1st paragraph in particular). Ibraghimov-Beskrovnaya *et al* teach that differential level of expression or absence of polycystin in different cysts suggests that loss of function is one mechanism of cystogenesis (page 6397 last paragraph). Due to the variable polycystin expression in cystic epithelial, ranging from levels more intense than in normal kidney, up to the absence of staining in some cysts, on skill in the art at the time the invention was made would not predict the efficacy of modulating cell-cell or cell-matrix adhesion in cysts using an agent such as an antibody against polycystin-1 to either enhance or inhibit cell-cell adhesion. The skilled in the art would not know when to inhibit cell-cell adhesion of cysts and when to enhance cell-cell adhesion in said cysts since the expression of polycystin-1 in said cysts can range between overexpressed to absent. The skilled in the art would not know how an agent such as an antibody would restore the loss of function with the claimed agents. "The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements...However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims." MPEP § 2164.03.

The specification on page 48, lines 17 to 28, discloses that an "agent" is intended to include, but not be limited to a biological or chemical compound such as a simple or complex organic or inorganic molecule, a peptide, a protein (e.g. antibody) or an oligonucleotide (e.g. anti-sense). The specification does not provide a sufficient enabling description of the claimed agents. A person of skill in the art is not enabled to make and use *any "agent"* including "agonists" or "antagonist" that modulates the binding of polycystin in the tissue as encompassed by the full breadth of the claims as currently recited. The term "agent" as recited encompass *any* agent that affects/modulates the function of polycystin. It was well known in the art at the time the invention was made that molecules having highly diverse structural and biochemical properties can function as "agonists" and "antagonists". However, Huang (Pharmacol. Therapeutics 2000 86:201-215) reviews in his "Introduction" on page 202 the daunting task faced by the skilled artisan in developing small molecule regulators of protein-protein interactions, and notes that the process required long periods of trial and error testing before suitable compounds could be developed. Similarly, Toole et al (Storming Media: the role of EMMPRIN in Tumor angiogenesis and metastasis, May 2001) teach that antisense cDNA and ribozyme constructs were utilized in an attempt to inhibit EMMPRIN expression TA3/ST cells, however, these constructs were not efficient in blocking EMMPRIN expression and consequently, were inactive in vivo (see the abstract in particular). Further, Mountain reviews in TIBTECH (18:119-128 2000) that while much progress has been made in the field of gene therapy, developing effective gene therapies is much more demanding than originally anticipated (e.g., pg 120, middle); and that most of the difficulty lies with the development of effective vectors since the vectors in use all have both advantages and disadvantages (e.g., Table 4). Mountain concludes that it is unlikely that a universal vector will emerge in the next few years (page 125, middle of 1st column). Similarly, although antisense therapy has progressed in recent years, there is still a high level of unpredictability in the art. This unpredictablity was summarized recently by Branch (TIBS 1998; 23:45-50). In particular, difficulties in ensuring that the oligo interacts with its single gene target versus other genes, and a variety of unexpected non-antisense effects, complicate the use of antisense compounds (e.g., summarized in Abstract). Finally, even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus in the absence of working examples or detailed guidance in the specification, the intended uses of any agent such as a simple or complex organic or inorganic molecule, a peptide, a protein (e.g. antibody) or an oligonucleotide (e.g. anti-sense) are fraught with uncertainties.

While "agent" of that modulates (agonist or antagonist) the binding of polycystin may have some notion of the function of the claimed molecules; there is insufficient biochemical or structural information to enable the skilled artisan to make and use the "agonists" or "antagonist" of polycystin protein, as broadly claimed. "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception

having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Given the unpredictability associated with identifying individual molecules which would function as "agonists" or "antagonist" that can modulate cell-cell or cell-matrix in the suitable tissue; the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 10/18/04, have been fully considered, but have not been found convincing

At the last paragraph of page 11 of the Brief, Applicant traverses the rejection on the basis that the Office has failed to meet its initial burden of providing a *prima facie* case to support the enablement rejection. Applicant states that the subject application was filed in 2001, and claims priority to there provisional applications filed during the course of 1998 and 1999. Applicant submits that the first Office Action provided a 1994 research article published at least 4 years prior to the earliest priority date claimed, to support its statements regarding the level of skill and the unpredictability in the art of antibody therapy. Applicant argues that the Ward *et al* reference published 4 years prior to the effective filing date cannot describe the state of the art at the time the priority applications wee filed (in 1998 or 1999) and therefore cannot be used to rebut Applicants' specification and evidence of record. Applicant further, submits that the Office has not provided any evidence that the general statements regarding the use of antibodies, directed against a different therapeutic target, is relevant to the claimed invention. Applicant submits that the Office provided no evidence with respect to the use of agents other than antibodies in practice of the claimed invention, e.g., polypeptides and oligonucleotides. Applicant's arguments have been fully considered but are not found to be persuasive. Regarding Ward et al, Applicant dismiss its teaching as "at least 4 years prior to the earliest priority date claim". However, applicant did not dispute the facts presented by Ward et al reference and contrary to the applicant assertion, the time may have changed, however, the antibody therapy standard has not changed. Applicant has not provided evidentiary art to refute the facts presented in the reference teachings.

Applicant submits on page 12 of the Brief that with respect to support for the scope of the claim term "agents", the specification provides sequence information and working examples of the use of proteins, polypeptides, oligonucleotides, polyclonal antibodies, and monoclonal antibodies that modulate cell-cell and cell-matrix interactions. Applicants further submits that they provided a detailed description and examples of agents that promote or enhance cell-cell or cell-

matrix adhesion (Applicant points to the specification on page 47, lines 21-27, lines 23-25, and lines 24-27, and page 48, line 29 to page 49, line 18). Applicant submits that the level of skill in the art at the time the invention was made, in combination with Applicants' specification, enables the full scope of the term "agent". Applicant's arguments have been fully considered but are not found to be persuasive. Applicant has not provided evidence to demonstrate that a skilled artisan would know how to make and use an agent that would promote or enhance cell-cell adhesion. For example, neither the Applicant nor the specification (page 6, lines 28-30) discloses how to make polynucleotide that modulates the binding of polycystin in a method for modulating cell-cell adhesion in a suitable tissue whether *in vivo* or *in vitro*. Undue experimentation would be required of the skilled artisan to obtain "agents" and determine their specific activity. Besides, antibodies to polycystin and the homophilic Ig-like domains Ig^a, Ig^b and Ig^c, the specification fails to provide sufficient direction or objective evidence as to how to make and use an agent which enhances cell-cell adhesion for the number of possibilities associated with the myriad of direct and indirect effects associated with various agents. Further, it is noted that the claimed "agent" employed in the various methods of modulating (inhibiting/enhancing) cell-cell adhesion do not share a substantial structural feature essential to a common function. One of ordinary skill in the art cannot envision all of the agents, which include antibodies, proteins, polypeptides and polynucleotides encompassed by the breadth of the claims and having a function in cell-cell adhesion. It is unclear whether such a desired effect can be achieved or predicted, as encompassed by the claims. Furthermore, in order to "modulate" cell-cell adhesion, the method requires inhibiting and activating agents. Said agents are mutually exclusive in that they reach opposing endpoints, and in that they employ structurally distinct agonists or antagonists to accomplish these mutually exclusive endpoints. The specification discloses that the claimed antibodies can be used for both inhibiting as well as promoting cell-cell adhesion. For example, the specification on page 47, lines 10- 27 discloses that the agent is any agent that inhibits polycystin-1 mediated cell-cell adhesion such agents include antibodies that bind to the Ig-like domains of polycystin or polycystin fragments comprising the Ig-like domains and agents that inhibit the expression of polycystin in a cell (e.g., antisense polycystin DNA and ribozymes that specifically recognize or cleave polycystin RNA in a cell). In addition, one can restore normal cell-cell (i.e. promote cell-cell adhesion) or cell-matrix adhesion in a tissue containing soluble, mutated polycystin by removing or binding the mutated polycystin using the anti-polycystin antibodies described in the invention (see page 47, lines 10- 27). Thus, faced with contradictory and seemingly mutually exclusive function regarding the activity of the claimed antibody, undue experimentation would be required of the skilled artisan to determine the effect of anti-polycystin on any particular cell-cell adhesion in vivo in view of the instant disclosure. Further, the enablement issues of making the proteins, polypeptides, polynucleotides still remain because the specification does not teach and provide sufficient guidance as to which amino acid or nucleic acids would retained the function of enhancing/inhibiting cell-cell adhesion. Therefore, absent the ability to predict which of these polypeptides, proteins or polynucleotides would function as claimed, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

At the end of page 12 of the Brief, Applicant addresses the issue that the specification does not adequately teach how to effectively reach any therapeutic endpoint in mammals by administrating the therapeutic antibody against polycystin nor teach how to extrapolate data obtained from *in vitro* model of disrupt cell-cell adhesion studies to the development of effective *in vivo* therapeutic treatment, commensurate in scope with the claimed invention. Applicant directs the Office's attention to the specification on page 42, line 23 to page 57, line 30 of the specification. Applicant submits that the specification on page 42, line 23 to page 57, line 30 teach how to make and use agents for their claimed purpose(s) and provides, a comparison of in vitro efficacy of several of the agents against the known interaction of p53 and SV40 large T antigen. Further, Applicant submits that the Office has failed to provide any evidence that the teachings of the specification was evaluated as it pertains to one of skill in the art at the time the application was filed or its earliest priority date. Regarding the lack of guidance and direction for disease or conditions for treatment by the claimed methods, Applicants direct the Office's attention to pages 2 and 3 of the specification. Applicant's arguments have been fully considered but are not found to be persuasive. Although Applicants' specification describes certain in vitro experiments, there is no correlation on this record between in vitro experiments and a practical function in currently available form for humans or animals. It is not enough to rely on in vitro studies where a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to function in humans or animals. See Ex parte Maas, 9 USPQ2d 1746. There must be a rigorous correlation of pharmacological activity between the disclosed in vitro function and an in vivo function to establish practical function. In the instant case the specification discloses the addition of GST-Ig^a, GST-Ig^b and GST-Ig^c to MDCK cell monolayers resulted in disruption of cell-cell adhesion. The exemplification is drawn to the disruption of cell-cell adhesion, *in vitro,* using fusion protein (pages 57). The claimed antibody was not used to show whether the anti-polycystin antibody would enhance or inhibit cell-cell adhesion. The specification fails to provide empirical data to show that method would work in vivo. In addition to the contradictory and seemingly mutually exclusive function regarding the activity of the claimed antibody, see above, undue experimentation would be required of the skilled artisan to determine the effect of anti-polycystin on any particular cell-cell adhesion in vivo in view of the instant disclosure. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use any agent such as the anti-polycystin antibody, and absence of working examples providing evidence which is reasonably predictive that the claimed method for promoting cell-cell adhesion are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed method with a reasonable expectation of success.

12. Claims 22, 27 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth in the previous Office Actions mailed 11/20/02 and 9/12/03 and is also fully set forth below.

Applicant is not in possession of a method for modulating cell-cell adhesion in any suitable tissue, comprising delivering to the tissue any agent that modulates the biding of polycystin in the tissue, wherein the modulation of cell-cell or cell-matrix adhesion is promotion or enhancement of cell-cell or cell-matrix adhesion in a suitable cell or tissue.

Applicant has disclosed only antibodies to polycystin and the homophilic Ig-like domains Ig^a, Ig^b and Ig^c that can inhibit cell-cell adhesion *in vitro*; therefore, the skilled artisan cannot envision all the contemplated agents including stimulatory antibodies such as that bind to mutated from or soluble form of polycystin that enhance cell-cell or cell-matrix adhesion recited in the instant claims. The specification further fails to disclose which simple or complex organic or inorganic molecule, peptide, protein (e.g. antibody) or oligonucleotide (e.g. anti-sense), can modulate the binding of polycystin in the tissue.

An adequate written description of a chemical invention requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described."). See MPEP 2163.

Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath

at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant's arguments, filed 6/12/03, have been fully considered, but have not been found convincing.

At the bottom of page 13 of the Brief, Applicant incorporates by reference the statement and evidence of record as described under Enablement rebuttal. In particular, the evidence of actual reduction to practice of numerous agents falling within the scope of the claims. Applicant submits that the specification establishes that they were in possession of the full scope of the invention at the time of its filing. Applicant's arguments have been fully considered but are not found to be persuasive because the Applicant has not provided evidence to demonstrate that the skilled artisan would be able to envision the detailed structure of the infinite number of agents encompassed in the claims. The description of GST-Ig^a, GST-Ig^b and GST-Ig^c for the disruption of cell-cell adhesion in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally agents. The specification and claims do not indicate what characteristics are shared by members of the genus of agents. The scope of the claims include numerous structural variants and the genus is highly variant because a significant number of structural differences between genus members is permitted. However, the specification does not provide any guidance as to what changes should be made and structural features that distinguish agents in the same genus from others are absent from the specification. The specification fails to disclose the common characteristics that identify members of the genus, and because the genus is highly variant, and GST-Ig^a, GST-Ig^b and GST-Ig^c are insufficient to describe the genus.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
January 10, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600